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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/009,685 | 04/23/2002 | Lars Reinhardt Haaheim | 061612-0015 | 8212 |

9629 7590 06/04/2007

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| EXAMINER | |
|---|---|
| GABEL, GAILENE | |
| ART UNIT | PAPER NUMBER |
| 1641 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 06/04/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/009,685 | HAAHEIM, LARS REINHARDT | |
| | Examiner | Art Unit | |
| | Gailene R. Gabel | 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 May 2007 and 11 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-22,24-29,31-42 and 47-49* is/are pending in the application.

4a) Of the above claim(s) *1-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,22,24-29,31-42 and 47-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-22,24-29,31-42 and 47-49* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 8, 2007 has been entered.

### *Amendment Entry*

2. Applicant's amendment and response filed on December 11, 2006 is acknowledged and has been entered. Claims 21, 22, 26, 31, 34, 35, and 40 have been amended. Claims 47-49 have been added. Claims 1-20 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected invention. Claims 1-22, 24-29, 31-42, and 47-49 are pending. Claims 21, 22, 24-29, 31-42, and 47-49 are under examination.

### *Withdrawn Rejections*

3. All rejections not reiterated herein, have been withdrawn.

4. In light of Applicant's amendment and arguments, the rejection of claims 21, 22, 24-29 and 31-42 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 21, 22, 24, 26-29, 31, 33-42, and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Choi (Biosynthesis and Secretion of Immunoglobulins, Immunoglobulins, pages 345, 346, 348-351 (1981)) or Atkinson et al. (Journal of Immunological Methods 76: 365-373 (1985)) in view of Cox et al. (Kinetics of early immune response induced after parenteral influenza vaccination (Options for the control of influenza III, 561-571 (1996)).

Choi provides methods used to study production of newly synthesized antibodies (biosynthesis of immunoglobulins) in lymph node samples in response to immunogen exposure (see Introduction). Choi teaches obtaining a lymph node tissue sample and isolating (purifying) lymphocytes from the sample using Ficoll-Hypaque gradient centrifugation (see page 345 second and third full paragraph). Thereafter, the lymphocytes are cultured and stored (chilled) at about 4 °C or less (ice water bath (2-6 °C)) to separate the cells from incubation media containing secreted proteins. The

lymphocytes are then lysed using nonionic detergent solution to solubilize cytoplasm without breaking the nuclei and to release newly synthesized proteins and antibodies. The released antibodies are detected using serological assay, which provides a measure of the amount of newly biosynthesized antibodies present in the lymphocytes present in the lymph node tissue sample (see page 346, first paragraph). Choi provides that secretion of newly synthesized antibodies (if secreted from lymphocytic cells) does not begin until 30 minutes after synthesis.

Atkinson et al. provide an enzyme-linked immunosorbent assay (ELISA) method for direct measurement of newly synthesized antibody being produced in immune cells, i.e. synthetic capacity, in response to immunogen exposure (anamnestic response to immunization). Atkinson et al. teach obtaining an immune spleen or lymph node sample containing lymphocytes from mice, isolating [nucleated] lymphocytic cells by Ficoll-Hypaque gradient centrifugation, eliminating [secreted] antibody carry-over by multiple washing of the lymphocytes, and lysing the cells using physical disruption (freeze-thaw method and sonication) to release newly synthesized antibodies from the cells. After preparation of the sample for assay, Atkinson et al. adds a sample volume of less than 1 ml. (200 µl) into multiple solid phases having one or more antigens immobilized thereto (antigen-coated wells) in a microtiter plate. One or more antibodies (biotinylated anti-mouse immunoglobulin) are also added and coated into the solid phase (see page 367 in its entirety). Atkinson et al. use highly sensitive avidin-biotinylated peroxidase (ABC) reagents and soluble substrate (orthophenylenediamine) to detect and measure the amount of newly synthesized antibodies by ELISA (see page 365, page 366, and

368 in their entirety). According to Atkinson, the lymphocytes should be stored and equilibrated at 4 °C after initial suspension in order to decrease the rate of antibody synthesis and secretion prior to the method (see page 369 in its entirety). Antibody production by different cell populations can be compared relative to standard controls included in each microtiter plate. Atkinson et al. teach using negative control antigen (irrelevant antigen or bovine serum albumin) as standard (see page 367).

Choi or Atkinson et al. have been discussed supra. Choi or Atkinson et al. differ from the instant invention in failing to teach detecting newly synthesized antibody in peripheral blood samples.

Cox et al. studies kinetics of early immune response induced after immunogen exposure (parenteral influenza vaccination). Cox et al. use different samples including peripheral blood, serum, and oral fluid. In study, in vitro cultures of peripheral blood lymphocytes were obtained and tested for antibody response to the immunogen exposure by detecting or determining for the presence of IgG, IgM, and IgA in the sample. See Abstract, page 565 (The antibody secreting cell response in peripheral blood), and page 567 (The antibody secreting cell response in tonsils).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to perform the method as taught by Choi or Atkinson on peripheral blood samples as taught by Cox because Cox provided that lymphocytes used in the method of Choi and Atkinson, can be obtained and cultured from peripheral blood samples for use in testing antibody production in response to parenteral influenza vaccination; hence, peripheral blood appears to constitute an obvious variation of

sample routinely used in the art, upon which lymphocytic cells can be obtained for use in antibody production assays.

6. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Choi (Biosynthesis and Secretion of Immunoglobulins, Immunoglobulins, pages 345, 346, 348-351 (1981)) or Atkinson et al. (Journal of Immunological Methods 76: 365-373 (1985)) in view of Sison A V (Laboratory Methods for early detection of HIV-type-1 in Newborns and Infants, (Clinical Microbiology Reviews, 5(3): pp. 238-247 (July 1992)).

Choi and Atkinson et al. have been discussed supra. Choi and Atkinson et al. differ from the instant invention in failing to teach detecting newly synthesized antibodies in neonate or infant blood samples to distinguish between newly synthesized antibodies from the infant and passively transferred maternal antibodies.

Sison teaches determining in vitro antibody production and using ELISA Spot assay to test for immunogenic exposure of infant or neonate to the HIV-1 virus. In practice, Sison teaches obtaining peripheral blood lymphocytes from infants, isolating and culturing the lymphocytic cells in vitro, subjecting the cells to immunogen activation, i.e. pokeweed, and detecting for the production or presence of anti-HIV-1 antibody using HIV-1 antigen coated solid phase (polystyrene wells). Sison uses this test to distinguish between newly synthesized antibodies from the infant and transferred maternal antibodies during pregnancy. See Abstract and page 241, column 1.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to detect newly synthesized antibodies using the method taught by

Choi or Atkinson on neonatal or infant blood samples as taught by Sison because Choi and Atkinson specifically taught that their methods specifically detect biosynthesis of antibodies in specific cells, such as those that are derived from neonatal cells as in the teaching of Sison, where he specifically emphasized the need to separate and distinguish between neonatal derived antibodies and maternally transferred antibodies. One of ordinary skill in the art at the time of the instant invention would have been motivated to detect for the presence of newly synthesized antibody using the method of Choi or Atkinson, in samples obtained from infants or neonates as taught by Sison, because Sison specifically taught that antibody production, i.e. of newly synthesized antibodies, in neonatal [lymphocytic] cells provides specific diagnostic information on immunogen exposure and infection for infants.

***Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 21, 22, 25, 48, and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining the presence of newly synthesized antibody in lymphocyte preparation isolated from whole peripheral blood sample comprising:

- obtaining the blood sample when lymphocytes are in acute phase of antibody synthesis in response to immunogen; and

- detecting said target antibodies or fragments thereof which are antigenically active, and produced within the lymphocyte in vivo, and released from lysed lymphocytes contained in the prepared sample; and wherein the sample is not incubated after blood collection and prior to the method;

does not reasonably provide enablement for a method in which the blood sample is collected when lymphocytes are not in acute phase of antibody synthesis in response to immunogen, as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As set forth in In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of the experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of prior art, the relative skill of those in the art, and the breadth of the claims.

In this case, the specification at page 7, first full paragraph, specifically provides that it is required that the sample is taken at a time when the lymphocytes of the subject's immune system are in acute phase of antibody synthesis in response to immunogen. According to Applicant's disclosure, it is found that sample is obtained within three weeks of presentation of the subject with the immunogen, preferably 8-12 days of infection or vaccination, and sufficiently 1-5 days or 2-3 days. The specification states that collection within the time frames are required in order to obtain meaningful

results in accordance with Applicant's invention. Nowhere in the specification does it teach a method such as recited in claims 21, 22, 25, 48, and 49, wherein the required time of collection is limited so as to obtain meaningful results in accordance to Applicant's invention.

***Response to Arguments***

8. Applicant's arguments filed December 11, 2006 have been fully considered but they are not persuasive.

A) Applicant argues that the combination of Atkinson or Choi with Cox does not render obvious the claimed invention because none of these cited references are directed to or encompass detection of newly synthesized antibodies that have been produced by lymphocytes in response to the presence of an immunogen in vivo as part of an ongoing immune response. Applicant contends that these antibodies are synthesized before and at the time the lymphocyte containing sample is removed from the subject animal, and are distinct from antibodies that are synthesized in vitro during incubation as set out in the assays described in Choi and Atkinson. Applicant specifically argues that by reciting, "newly synthesized antibodies" in the claims as defined in the instant specification, use of long incubation times are implicitly excluded.

In response, Applicant's argument is not persuasive because further definition of "newly synthesized antibodies" in the Applicant's specification provides that the definition generally corresponds to antibodies produced in the preceding 2 hours which may occur exclusively in vivo or at least partially in vitro prior to cell disruption if cells

are under appropriate conditions (page 6, first full paragraph). Hence, the rejected claims do not exclude any amount of incubation times encompassed and taught by Choi or Atkinson. Further responsive to Applicant's argument, the cell-based ELISA modification as taught by Choi and Atkinson and combined with Cox, provides a measure of newly synthesized antibodies as claimed because the recited steps of detecting target antibodies released from lysed lymphocytes contained in a prepared lymphocyte sample, are not limited to antigenically active antibodies produced and synthesized by and within lymphocytes in vivo, and as such, the claimed method is still deemed to be consonant to that taught by Choi and Atkinson.

B) Applicant argues that since Choi and Atkinson require incubation periods of the lymphocyte sample prior to testing, it follows that the combination of references does not disclose or suggest that lymphocytes would contain enough antibody to be able to detect the antibody without performing long in vitro incubations with antigen. Applicant contends that the long incubations allow antibody in the method of Choi or Atkinson that is synthesized in vitro to build up in culture medium. Applicant then states that simply lysing cells directly from a blood sample (as taught in Applicant's invention) would not be expected to yield detectable levels of antibody.

In response, Applicant's argument is not persuasive because again, the definition of "newly synthesized antibodies" in the Applicant's specification provides that the definition generally corresponds to antibodies produced in the preceding 2 hours which may occur exclusively in vivo or at least partially in vitro prior to cell disruption if cells

are under appropriate conditions (page 6, first full paragraph). Hence, the rejected claims do not exclude any amount of incubation times encompassed and taught by Choi or Atkinson. Additionally, the methods as taught by Choi and Atkinson and combined with Cox, provides a measure of newly synthesized antibodies as claimed because the recited steps of detecting target antibodies released from lysed lymphocytes contained in a prepared lymphocyte sample, are not limited to antibodies produced and synthesized by and within lymphocytes in vivo; and wherein the antibodies are collected during acute phase of antibody synthesis in response to immunogen as defined in Applicant's disclosure at page 7, first full paragraph. The specification states that collection within the time frame of acute antibody synthesis in response to immunogen activation, is required in order to obtain meaningful results in accordance with Applicant's invention. Therefore, consonant to that taught by Choi and Atkinson, simply lysing cells directly from a blood sample, when performed without incubation prior to detection such as claimed, would not be expected to yield detectable levels of antibody, unless otherwise collected during acute phase antibody synthesis in response to immunogen. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
May 27, 2007